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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB88/00779  <b>(22) International Filing Date:</b> 22 September 1988 (22.09.88)  <b>(31) Priority Application Number:</b> 8722306  <b>(32) Priority Date:</b> 22 September 1987 (22.09.87)  <b>(33) Priority Country:</b> GB  <b>(71) Applicant (for all designated States except US):</b> APS RE- SEARCH LIMITED [GB/GB]; Whitcliffe House, Whitcliffe Road, Cleckheaton, West Yorkshire BD19 3BZ (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> BARRY, Brian, William [GB/GB]; 23 Dales Way, Tranmere Park, Guiseley, Leeds LS20 8JN (GB). MULLEY, Bryan, Arthur [GB/GB]; 10 Yew Tree Avenue, Bradford, West Yorkshire BD8 0AD (GB). YORK, Peter [GB/ GB]; 24 Parish Ghyll Road, Ilkley, Yorkshire (GB).		<b>(74) Agent:</b> PENNANT, Pyers; Stevens, Hewlett & Perkins, 5 Quality Court, Chancery Lane, London WC2A 1HZ (GB).  <b>(81) Designated States:</b> AT (European patent), BE (Euro- pean patent), CH (European patent), DE (European patent), FR (European patent), GB (European pa- tent), IT (European patent), JP, LU (European pa- tent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SUSTAINED-RELEASE NIFEDIPINE FORMULATION  <b>(57) Abstract</b>  A sustained-release nifedipine (4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine) formula- tion comprising sufficient granules to provide a predetermined dose or number of doses of nifedipine, each of said gra- nules having a diameter of between 0.5 and 2.5 mm and comprising: (a) a core comprising 100 parts of nifedipine and from 50 to 800 parts of hydroxypropylmethyl cellulose; and (b) a coating covering substantially the whole surface of the core and comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative, the weight of the coating being from 2 to 25 % of the weight of the core. A meth- od for preparing the formulation is also provided.		

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SUSTAINED-RELEASE NIFEDIPINE FORMULATION

This invention relates to a sustained-release formulation containing nifedipine and, most preferably, to such a formulation which will provide sustained-release of the nifedipine over a period of about twelve  
5 hours. A method for preparing the sustained-release formulation is also provided.

Some medical conditions are best treated by administration of a pharmaceutical which is formulated to allow the active substance or ingredient to act as  
10 quickly as possible. Such a formulation may comprise an injectable solution or a readily dissolvable tablet or capsule. This type of formulation is useful, for instance, for treating acute pain, such as headaches, or pain associated with sudden trauma, such as an  
15 accident.

Other medical conditions are best treated by administration of a pharmaceutical in such a way as to sustain its action over an extended period of time. This type of administration is useful, for example, for  
20 treating chronic pain, such as that associated with rheumatic or arthritic conditions, or for the treatment of a chronic cardiovascular condition. It can be achieved by repeated administration of an immediate-release tablet or capsule at frequent intervals, for instance  
25 every four hours. However, this is generally inconvenient, especially during the night, when it is often necessary to awaken a patient to administer the tablet or capsule.

It has previously been proposed to produce a  
30 formulation which will release the active substance therein at a controlled rate such that the amount available in the body to treat the condition is maintained at a relatively constant level over an extended period of time. A particularly suitable period

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is twelve hours, since such a formulation need only be taken twice a day to maintain an effective treatment of the condition. Such formulations are generally known as "sustained-release formulations."

5 Many sustained-release formulations are already known, but there is no generally applicable method by which such formulations can be designed. Each formulation is dependent on the particular active substance incorporated therein. In designing a  
10 formulation, it is generally necessary to take into account many factors, including the rates of absorption and clearance of the active substance, the interaction of the active substance with the excipients and/or coatings to be used in the formulation, the solubility  
15 of the excipients and/or coatings, and the effects on the bioavailability of the active substance which may be caused by the excipients and/or coatings. It is, however, not possible readily to predict whether any particular formulation will provide the desired  
20 sustained-release, and it is generally found necessary to carry out considerable experimentation to produce a sustained-release formulation having the desired properties.

Nifedipine is the generic name for 4-(2'-  
25 nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine. It is a vasodilator known to be useful for the treatment of hypertension and angina pectoris. Nifedipine is practically insoluble in water and has proved difficult to formulate effectively for oral  
30 administration. British Patent No. 1,173,862 relates to nifedipine itself and describes preparations thereof, optionally in admixture with an inert liquid or solid diluent or carrier, in the form of tablets and pills. These preparations have the disadvantage of a  
35 very slow and unpredictable rate of absorption from the gastrointestinal tract.

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U.S. Patent No. 3,784,684 describes oral-release capsules which are prepared by dissolving nifedipine using a solubilising agent and enclosing the solution in a capsule. The capsules provide a very  
5 rapid release of the nifedipine in a form which is readily absorbable by the body. However, liquid preparations in capsules are much more inconvenient to produce than solid preparations. Further, because of the low solubility of nifedipine, a large amount of the  
10 solubilising agent is required and so the unit doses, and thus the capsules containing them, are inevitably large. This is obviously a disadvantage with preparations intended for oral administration.

European Patent Application No. 0001247 relates  
15 to pharmaceutical preparations for oral administration which comprise either a solution of nifedipine in polyethylene glycol or a non-crystalline dispersion of nifedipine in polyvinylpyrrolidone. These preparations are said to be stable and to present nifedipine in a  
20 form which is easily and rapidly absorbable by the body.

British Patent No. 1,579,818 describes various solid pharmaceutical preparations containing nifedipine. These include preparations which comprise a  
25 mixture of nifedipine and one or more of methyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose, optionally together with other components. The preparations are produced by a method which involves dissolving the ingredients in an  
30 organic solvent, which is then extracted leaving a solid composition or a powdery solid composition. The resulting preparations show a rapid release of the nifedipine and are said to show the same high bioavailability within the body as the previously  
35 mentioned liquid preparations. There is no teaching or suggestion that the preparations could be formulated

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with a coating for achieving sustained-release properties.

5 A sustained-release formulation containing nifedipine is currently marketed in the United Kingdom under the name Adalat Retard (a registered trade mark). However, this formulation does not provide as good a sustained-release as is desirable. There is therefore a need for an improved sustained-release nifedipine formulation and particularly one having good sustained-  
10 release over a period of twelve hours. The present invention is based on the discovery of such an improved sustained-release formulation.

According to the present invention there is provided a sustained-release nifedipine formulation  
15 comprising sufficient granules to provide a predetermined dose or number of doses of nifedipine, each of said granules having a diameter of between 0.5 and 2.5 mm and comprising:

20 a) a core comprising 100 parts of nifedipine and from 50 to 800 parts of hydroxypropylmethyl cellulose; and

25 b) a coating covering substantially the whole surface of the core and comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative, the weight of the coating being from 2 to 20% of the weight of the core.

30 The invention further provides a method for preparing a sustained-release formulation and which comprises:

- 35 i) mixing nifedipine with hydroxypropylmethyl cellulose;
- ii) forming the mixture into core particles comprising 100 parts of nifedipine and from 50 to 800 parts of hydroxypropylmethyl cellulose;
- iii) forming a solution comprising 100 parts of a

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water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative; and

5 iv) coating the said core particles with the said solution to form granules having a diameter of between 0.5 and 2.5 mm.

In the following description, all parts and percentages are by weight unless otherwise indicated.

10 It will be appreciated that to some extent the diameter of the granules, the composition of the core and the composition and amount of coating will depend on the time over which the formulation is designed to work. Generally, however, each of the granules will have a diameter of between 0.5 and 2.0 mm, preferably  
15 between 0.7 and 1.2 mm. For every 100 parts of nifedipine present in the core, there will be from 50 to 800 parts of hydroxypropylmethyl cellulose. The core most preferably contains from 60 to 400 parts of hydroxypropylmethyl cellulose, more particularly from  
20 80 to 150 parts. For every 100 parts of the water insoluble but water swellable acrylic polymer present in the coating, there will preferably be from 20 to 70 parts of the water-soluble hydroxylated cellulose derivative. The weight of the coating will  
25 usually be from 2 to 25% of the weight of the core.

For a formulation designed to provide sustained-release over a period of 24 hours, the granule diameter is preferably between 1.5 and 2.0 mm, the coating preferably contains 20 to 70 parts of the  
30 water soluble hydroxylated cellulose derivative, and the weight of the coating is from approximately 5 to 25% of the weight of the core.

For a formulation designed to provide sustained-release over a period of 12 hours, the  
35 granule diameter is between 0.7 and 1.2 mm, the coating preferably contains 20 to 70 parts of the water soluble

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hydroxylated cellulose derivative, and the weight of the coating is preferably between 5 and 15% of the weight of the core.

5 In addition to nifedipine and hydroxypropylmethyl cellulose, the core also preferably contains a bulking agent such as microcrystalline cellulose. This is a well known form of cellulose which is partially depolymerised. A particularly suitable microcrystalline cellulose is sold under the name Avicel (a registered  
10 trade mark). However, other conventional bulking agents may also be used, as will be readily apparent to those skilled in the art.

The core may also contain a diluent, such as lactose. A capillary-active agent, such as sodium  
15 carboxymethylcellulose, which is sold under the name Ac-Di-Sol (a registered trade mark), may additionally be included. These components are used in conventional amounts. If desired, the formulation of this invention may also contain colouring agents, sweetening agents  
20 and flavouring agents.

The coating preferably comprises about 30 parts of the hydroxylated cellulose derivative. If too much is present, the coating may become too sticky and the rate of release may become too high. If too little is  
25 present, the rate of release may be too low. A particularly suitable hydroxylated cellulose derivative is hydroxypropylmethyl cellulose having a degree of substitution of 28 to 30% of methoxy groups and 7 to 12% of hydroxy groups. However, other equivalent  
30 materials such as hydroxypropyl, hydroxyethyl or hydroxymethyl celluloses can be used.

The acrylic polymer component of the coating is preferably neutral and may comprise a homopolymer or a copolymer, for instance of acrylic acid esters or  
35 methacrylic acid esters. Preferably, the acrylic polymer is provided as an aqueous dispersion. A particularly suitable acrylic polymer is sold under the



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name Eudragit (a registered trade mark), which comprises a copolymer of acrylic and methacrylic acid esters and which is usually supplied as an aqueous dispersion containing approximately 30% solids.

5           The formulation of this invention can be prepared in the following manner. The nifedipine is micronised (to increase its surface area and thereby improve dissolution) and then blended with the hydroxypropylmethyl cellulose and any other  
10 constituents of the core, such as a bulking agent, a diluent and a capillary-active agent. Alternatively, the nifedipine and the hydroxypropylmethyl cellulose may be mixed and then micronised, prior to blending with the other constituents. The blending is conveniently  
15 performed by mixing the components together with some water to produce a slightly cohesive product. This is then extruded, chopped into suitable lengths, spheronised and dried to form the core particles of the formulation. The particles may then be sieved. The coating  
20 is prepared by forming a solution of the hydroxylated cellulose derivative and mixing it with a dispersion of the acrylic polymer. The aqueous mixture is then used to coat the dried core particles, and the coated particles are subsequently dried to produce the granules. Preferably,  
25 the coated granules are then sieved to ensure that they are in the correct size range.

          The resulting granules may be supplied loose with a means for dispensing a measured amount of granules, for instance to be sprinkled on food.  
30 Alternatively, the granules may be provided in sachets containing measured amounts. More preferably, however, the granules are placed in measured amounts in readily soluble capsules. The capsule may be any of those already known in the art, and may, for instance,  
35 comprise a thin gelatin skin. Preferably, the capsule

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contains sufficient granules to provide a dose of 10, 20 or 40 mg of nifedipine. The granules may, if desired, be formed into tablets using conventional tabletting machinery, although it should be recognised that normal tabletting processes would be likely to damage at least some of the coated granules.

It has surprisingly been found that by the above set out selection of the materials for the core and the coating, the relative amounts of the components, and the size of the granules, it is possible to produce a sustained-release nifedipine formulation which shows effective sustained-release over any desired period and, in particular, over a twelve hour period. While not wishing to be limited by any mechanism, the inventors believe that the sustained-release properties shown by the formulation are achieved as follows. Upon being administered orally, the contents of the core of each granule is thought to dissolve quickly. It is the polymeric coating around the core which limits the subsequent release of the components of the core and hence produces the controlled sustained-release shown by the formulation.

One embodiment of the present invention will now be described, by way of example only, with reference to the accompanying drawing. Figure 1 shows the comparative in vitro dissolution profiles of a previously known formulation (Adalat Retard) and the formulation of the present invention (Apsipine 30/5).

#### 30 Example

The formulation described below (designated Apsipine 30/5) was developed using the OSAT system developed by the inventors at the University of Bradford.

The formulation was prepared from the following

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Core

	Nifedipine	10%	w/w
5	Hydroxypropylmethyl cellulose (Pharmacoat 603)	10%	w/w
	Avicel PH 101	39%	w/w
	Lactose	39%	w/w
	Ac-Di-Sol	2%	w/w
	Water	<hr/> q.s	

10

Coating

	Eudragit NE30D	5 parts
	Hydroxypropylmethyl cellulose (Pharmacoat 603)	1.5 parts

- 15 Core - Micronised nifedipine and the hydroxypropylmethyl cellulose, Avicel, lactose and Ac-Di-Sol were mixed together by doubling up in a dry blender. Water was added in portions until a slightly cohesive product was formed. The cohesive product was
- 20 passed through an extruder and the extruded material was chopped to produce slugs having a diameter of about 1mm and a length of 2 to 3 mm. The slugs were spheronised by passage through a spheroniser, and the particles thus formed were dried to constant weight at
- 25 60°C. The dried particles were sieved to separate those

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having diameters between 0.7 and 1.5 mm.

Coating - The hydroxypropylmethyl cellulose was dissolved in hot water and cooled. The cooled solution was mixed with the Eudragit NE30D and the mixture was diluted with  
5 further water to produce a coating mixture containing 0.2 g solids per gram of mixture.

The sieved core particles were rotated in a small coating pan and the coating mixture was added in portions to the pan until the weight of solids in the  
10 added coating mixture was 5% of the weight of the core particles. After each portionwise addition of coating mixture, air was blown into the pan to assist in water removal. At the end of the addition of the coating mixture, the coated core particles were dried to  
15 constant weight and sieved to produce granules having a size between 0.8 and 1.2 mm.

Hard gelatin capsules were each filled with the granules, to produce a total dose of 20 mg of nifedipine per capsule.

20 In vitro experiments were then carried out to determine the release properties of this formulation in comparison to Adalat Retard. The dissolution test used was the USP basket method, pH 6.8, flat-bottomed flask, temperature of 37°C, detector wavelength 238 nm,  
25 optical density of 3 mg/l nifedipine solution = 0.171. The results are shown in Figure 1. The release properties of the formulation of the present invention (designated Apsipine 30/5) and Adalat Retard were monitored for 10 hours. From the resulting dissolution profiles of Figure 1,  
30 it is clear that the formulation of the present invention shows rather faster initial release of the nifedipine, good subsequent sustaining release and increased total release after 10 hours.

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It will be appreciated from the above data that the formulation of the present invention provides a much improved sustained-release formulation compared with those previously available.

5           It will be appreciated that the present invention has been described above by way of illustration only, and it will be clear that variations and alterations of detail may be made by the man skilled in the art without departing from the scope of  
10 the invention.

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CLAIMS

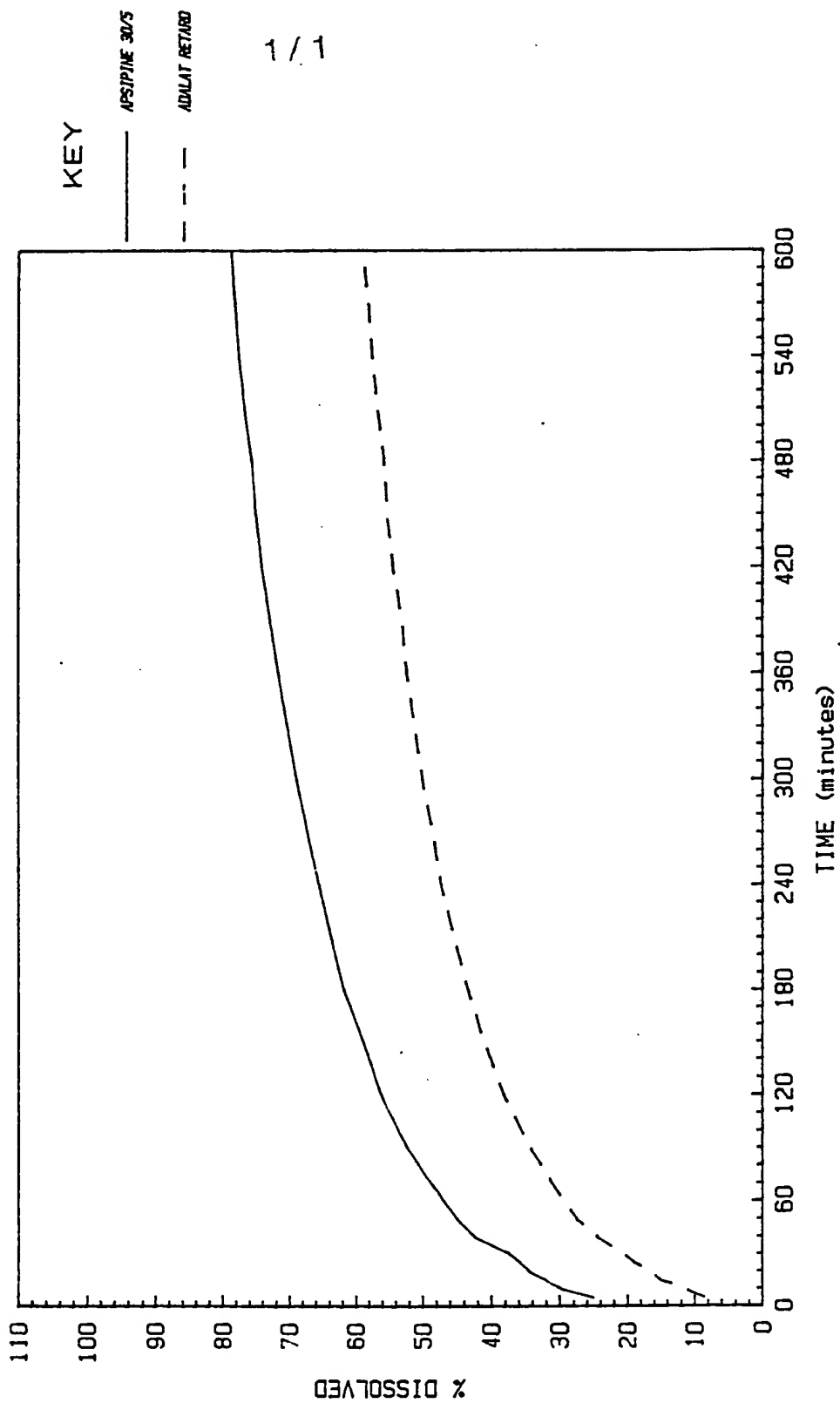
1. A sustained-release nifedipine formulation comprising sufficient granules to provide a predetermined dose or number of doses of nifedipine, each of said granules having a diameter of between 0.5 and 2.5 mm and comprising:
  - (a) a core comprising 100 parts of nifedipine and from 50 to 800 parts of hydroxypropylmethyl cellulose; and
  - (b) a coating covering substantially the whole surface of the core and comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative, the weight of the coating being from 2 to 25% of the weight of the core.
2. A formulation as claimed in claim 1, which provides sustained-release over a period of 12 hours, wherein the diameter of the granules is between 0.7 and 1.2 mm, the coating contains from 20 to 70 parts of the water soluble hydroxylated cellulose derivative, and the weight of the coating is between 5 and 15% of the weight of the core.
3. A formulation as claimed in claim 1, which provides sustained-release over a period of 24 hours, wherein the diameter of the granules is between 1.5 and 2.0 mm, the coating contains from 20 to 70 parts of the water soluble hydroxylated cellulose derivative, and the weight of the coating is from 5 to 25% of the weight of the core.
4. A formulation as claimed in any one of the preceding claims, wherein said core contains from 80 to 150 parts of hydroxypropylmethyl cellulose.

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5. A formulation as claimed in any one of the preceding claims, wherein said coating contains 30 parts of the hydroxylated cellulose derivative.
6. A formulation as claimed in any one of the preceding claims, wherein the hydroxylated cellulose derivative in the coating is hydroxypropylmethyl cellulose having a degree of substitution of 28 to 30% of methoxy groups and 7 to 12% of hydroxy groups.
7. A formulation as claimed in any one of the preceding claims, wherein the acrylic polymer in the coating is neutral.
8. A formulation as claimed in any one of the preceding claims, wherein said granules are contained within a capsule.
9. A method for preparing a sustained-release nifedipine formulation and which comprises:
  - i) mixing nifedipine with hydroxypropylmethyl cellulose;
  - ii) forming the mixture into core particles comprising 100 parts of nifedipine and from 50 to 800 parts of hydroxypropylmethyl cellulose;
  - iii) forming a solution comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative; and
  - iv) coating the said core particles with the said solution to form granules having a diameter of between 0.5 and 2.5 mm.
10. A method as claimed in claim 9, wherein the granules are sieved after formation.

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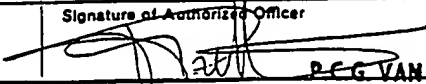
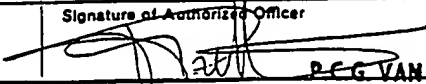
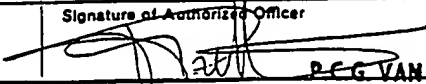
FIGURE 1. COMPARISON OF THE DISSOLUTION PROFILES  
OF APSIPINE 30/5 AND ADALAT RETARD





# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 88/00779

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>4</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>4</sup> :      A 61 K 31/44; A 61 K 9/52																	
<b>II. FIELDS SEARCHED</b> <div style="text-align: right; font-size: small;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%; border: none;">Classification System  </td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; vertical-align: top;">IPC<sup>4</sup></td> <td style="border: none; vertical-align: top;">A 61 K</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup></div>			Classification System	Classification Symbols	IPC <sup>4</sup>	A 61 K											
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IPC <sup>4</sup>	A 61 K																
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse; font-size: x-small;"> <thead> <tr> <th style="width: 10%;">Category <sup>10</sup></th> <th style="width: 70%;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 20%;">Relevant to Claim No. <sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A, 0123470 (ELAN CORPORATION PLC) 31 October 1984 see claims 1-9 --</td> <td></td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A, 0142561 (KANEBO LTD) 29 May 1985 see page 6, line 14 - page 9, line 3 --</td> <td></td> </tr> <tr> <td style="text-align: center; vertical-align: top;">P, A</td> <td>EP, A, 0255404 (APS RESEARCH LTD) 3 February 1988 see column 2, line 17 - column 3, line 30 --</td> <td></td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>WO, A, 86/01717 (PHARMATEC SpA) 27 March 1986 see page 2, line 14 - page 4, line 20 -----</td> <td></td> </tr> </tbody> </table>			Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	A	EP, A, 0123470 (ELAN CORPORATION PLC) 31 October 1984 see claims 1-9 --		A	EP, A, 0142561 (KANEBO LTD) 29 May 1985 see page 6, line 14 - page 9, line 3 --		P, A	EP, A, 0255404 (APS RESEARCH LTD) 3 February 1988 see column 2, line 17 - column 3, line 30 --		A	WO, A, 86/01717 (PHARMATEC SpA) 27 March 1986 see page 2, line 14 - page 4, line 20 -----	
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<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>																	
<b>IV. CERTIFICATION</b> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;">           Date of the Actual Completion of the International Search  <div style="text-align: center; font-weight: bold;">30th November 1988</div> </td> <td style="width: 50%; border: none; vertical-align: top;">           Date of Mailing of this International Search Report  <div style="text-align: center; font-weight: bold;">23. 12. 88</div> </td> </tr> <tr> <td style="border: none; vertical-align: top;">           International Searching Authority  <div style="text-align: center; font-weight: bold;">EUROPEAN PATENT OFFICE</div> </td> <td style="border: none; vertical-align: top;">           Signature of Authorized Officer  <div style="text-align: center;">   <b>P. G. VAN DER PUTTEN</b> </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; font-weight: bold;">30th November 1988</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold;">23. 12. 88</div>	International Searching Authority <div style="text-align: center; font-weight: bold;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center;">   <b>P. G. VAN DER PUTTEN</b> </div>											
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 8800779

SA 24363

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 13/12/88  
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0123470	31-10-84	BE-A- 899464 CH-B- 661434	16-08-84 31-07-87
EP-A- 0142561	29-05-85	JP-A- 58046019 WO-A- 8403440	17-03-83 13-09-84
EP-A- 0255404	03-02-88	JP-A- 63107917	12-05-88
WO-A- 8601717	27-03-86	AU-A- 4959485 JP-T- 62500660 EP-A- 0226588	08-04-86 19-03-87 01-07-87